CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 040135

Trade Name : ESTROPIPATE TABLETS

Generic Name: Estropipate Tablets

Sponsor : BARR LABORATORIES, INC.

Approval Date: NOVEMBER 27, 1996

ANDA 40-135

Barr Laboratories, Inc.
Attention: Christine A. Mundkur
2 Quaker Road
P.O. Box D2900
Pomona, NY 10970-0519

Dear Madam:

This is in reference to your abbreviated new drug application dated February 9, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Estropipate Tablets USP, 0.75 mg, 1.5 mg, and 3 mg.

Reference is also made to your amendments dated June 28, and October 28, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Estropipate Tablets USP, 0.75 mg, 1.5 mg, and 3 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Ogen® 0.75 mg, 1.5 mg, and 3 mg of Abbott Laboratories). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

D. L. Sporn 11/27/96

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA #40-135
ANDA #40-135/Division file
Field Copy
HFD-600/Reading file
HFD-82
HFD-8/P.Savino
HFD-610/J.Phillips

Endorsements:

R Permisohn 11/25/96
HFD-625/R.Permisohn/11-12-96
HFD-613/C.Holquist/11-18-96
HFD-610/J.Grace/11-19-96 11/22/96
HFD-625/M.Smela/11-13-96
HFD-617/S.Okeefe, CSO/11-18-96 11/25/96
x:\new\firmsam\barr\ltrs&rev\40135ap.d
F/T by MM November 20, 1996
Approval

11/27/96 F. Phillips 11/26/96

1. CHEMISTRY REVIEW NO.
11/25/96 8 2 3

2. ANDA
40-135

3. NAME AND ADDRESS OF APPLICANT
Barr Laboratories, Inc.
2 Quaker Road
Pomona, NY

4. LEGAL BASIS FOR SUBMISSION
21 CFR 505(j)

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Estropipate

8. SUPPLEMENT(s) PROVIDE(s) FOR
N/A

9. AMENDMENTS AND OTHER DATES

FIRM	FDA
Original dated **2/9/95.**	Acknowledgement letter dated **3/8/95.** NA letter dated **7/24/95.** BIO NA letter dated **8/22/95.**
Bio NC dated **10/24/95** Amendment dated **2/7/96.**	BIO letter dated **4/9/96.** NA letter dated **6/14/96.**
NC dated **6/28/96*.** Amendment dated **10/28/96***	

10. PHARMACOLOGICAL CATEGORY
Estrogen

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
83-220 (Abbott Ogen®)

13. DOSAGE FORM
Tablets

14. POTENCY
0.75 mg, 1.5 mg, 3 mg

15. CHEMICAL NAME AND STRUCTURE
Estra-1,3,5(10)-trien-17-one,3-(sulfooxy)-,compound with peperazine 1:1

See *USP 23* for structure.

16. RECORDS AND REPORTS
N/A

17. COMMENTS
In the original filing, Barr Laboratories had identified

as an outside contract testing laboratory. pleaded guilty of one (1) count of a violation of 18 U.S.C. Section 1505, resulting from a conviction of a former employee. However, had not been used to develop any of the data in the ANDA submission per Barr. Copies of the Debarment Certification Statements and Lists of Convictions for and other outside testing laboratories have been provided.

Labels/labeling are in Vol. 1.1, on pp. 28-79. Revised labels/labeling are found on pp. 05-00001 ff. of the **2/7/96**, amendment.

CMC information are in Vol. 1.5 and 1.6, on pp. 2005-3042 of the original filing. The amendment dated **2/7/96**, contains information for two additional dosage strengths of 0.75 mg, and 1.5 mg. Additionally, the firm's response to our NA letter dated **7/24/95**, is contained therein. Documentation for the 0.75 mg and 1.5 mg tablets are provided, as is appropriate, in the firm's responses to deficiencies for the 3 mg tablets. Outstanding isssues were addressed in our NA letter dated **6/14/96**.

The results of a single dose, two-way crossover *in vivo* bio study are in Vol. 1.1-1.4, on pp. 80-2004. The firm's **10/24/95**, amendment addressed the BIO NA letter dated **8/22/95**. The Gur J. P. Singh bio review dated **4/4/96**, includes the Recommendations such that "The *in-vivo* bioequivalence study conducted under fasting condition by Barr Laboratories on its estropipate 3 mg tablet, lot #4R72903 comparing it to the reference product Ogen® 3 mg tablet, lot #73820AA21, manufactured by Abbot, has been found to be acceptable to the Division of Bioequivalence...The formulations for estropipate 0.75 mg and 1.5 mg tablets are proportionally similar to the 3 mg tablet of the test product which underwent bioequivalence testing. The waivers of *in vivo* bioequivalence study requirements for 0.75 mg and 1.5 mg tablets of the test product are granted...The dissolution testing should be incorporated into firm's manufacturing and stability programs. The dissolution should be conducted in 900 mL of water using USP XXII apparatus II (paddles) at 75 rpm. The dissolution testing should meet the following specifications.

> Not less than of the labeled amount of estropipate is dissolved from the dosage form in 60 minutes.

From the bioequivalence point of view, the firm has met the requirements for *in vivo* bioequivalence and *in vitro* dissolution testing."

The bio letter dated **4/9/96**, notified the applicant that

there were no further questions at that time. Also, the dissolution parameters for QC and stability testing were presented to the firm.

OGD DOB summary dated **4/12/96**, concludes that the 3 mg tablet is bioequivalent to the reference product, and that the "Waivers for the 0.75 mg and 1.5 mg tablets ar granted.". Also, "...The dissolution testing meets the USP specifications.".

NC dated **6/28/96:** This provides a response to our BIO letter dated **4/9/96**. Barr acknowledged that the DOB has completed its review, and has no further questions at that time. Barr stated that the recommended dissolution parameters have been incorporated into the stability and qc programs. According to Barr, these were incorporated into the Quality Control and Stability Program on **10/11/94**. Included are the current (as of **6/28/96**) Acceptance Test for In-Process & Finished Product, Quality Control Analytical Test Record for Estropipate Tablets, *USP*, and the Marketed Stability Specification Test Record for Estropipate Tablets *USP* for the 0.75 mg, 1.5 mg, and 3 mg dosage strengths.

Amendment dated **10/28/96:** This addresses our NA letter dated **6/14/96**, which discussed outstanding issues from our NA letter dated **7/24/95**, and the firm's response to same dated **2/7/96**. The comment citations in our NA letter dated **6/14/96**, were drawn from our NA letter dated **7/24/95**.

Comment 1. referred to Barr's responses for comments 1.a. and 1.b. of our cited letter, which addressed physical characteristics of the ds. We recommended that blend analyses and material adhering to processing equipment continue to be monitored. Barr made a commitment to perform in-process testing for blend content uniformity for each dosage strength. After sufficient blend uniformity data have been attained, Barr will supplement the ANDA to delete blend testing. The Quality Control Analytical Specification Test Records used for release and the In-Process and Finished Product Test Method have been revised to include blend content uniformity testing and specs. Barr has made a commitment to monitor the potency of estropipate in blend and the finished products.

Comment 2.a. referred to response 6.a., of Barr's **2/7/96**, cover letter in which a target with a range of was declared, whereas, on pp. **00-00040, 00-00041, 00-00049,00-00050, 00-00051,** and **00-00052** for the Master, the target is with a range of . Barr was asked to identify the correct specs. Barr stated that the spec. in the cover letter was a typo error. The spec. with a target of with a range of in the Master is correct.

Comment 2.b. cited comment 6.e., which recommended that Barr continue to monitor each batch for as per comment 1. of our NA letter. Barr concurs, and referred to its response to comment 1.

Comment 2.c. referred to comment 6.g., in which we recognized that Barr will discontinue testing from the stability program for future production batches. We informed Barr that the test is still to be performed on the finished product, and for stability purposes per Method TM-332F, and asked for clarification of whether or not the test would be performed. Barr stated that the test for will not be performed, and has submitted the current Quality Control Analytical Specification Test Records and Marketed Stability Specification Test Records for the products reflecting the revisions. Also, the Marketed Stability Protocol, similarly, has been revised. However, Barr will continue to monitor for 24 mos. for the demonstration batches of each dosage strength.

Comment 3. related to the firm's response to comment 9.b., in which Barr concurred after their review of the available stability data that it would be appropriate to reduce the specification for any Individual Impurities/Degradants other than Estrone to NMT We again recommended that this specification of NMT be used at the time of release and for stability purposes for the drug products. Also, we noted that a reasonable effort would be made to identify impurities of "significant magnitude", and asked the firm to declare the threshold that was associated with "significant". Barr has agreed to reduce the spec. for any individual impurity/degradant other than Estrone to NMT at the time of release and for stability purposes. Barr will make a resonable effort to identify any impurity/degradant MT

Labeling Deficiencies:

FPL container labels for 21s, 100s and 1000s, and professional and patient insert labeling were submitted. These are satisfactory per C. Holquist Approval Summary dated 11/4/96. Included in the summary is a "Note to the Chemist" in which it was pointed out that the innovator labels/labeling bear a storage instruction to "store below 25°C", whereas, the Barr products will be stored at 15°C-30°C. C. Holquist asked if there are data in support of the Barr storage conditions. The previously submitted data tentatively support the Barr labeled storage conditions.

Barr was asked to note and acknowledge the following in their response:

1. Comment 2. of our cited letter (i.e., CGMP compliance

of all facilities) is still pertinent. Barr acknowledged same.

2. We asked for concurrence with the Division of Bioequivalence dissolution testing recommendation in their letter dated **4/9/96**. Barr acknowledged same.

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend Approval

19. REVIEWER
Robert C. Permisohn

DATE COMPLETED
11/8/96

cc: ANDA #40-135
ANDA #40-135/Division File
Field Copy

Endorsements:

11/25/96

HFD-625/RPermisohn/11-8-96
HFD-625/MSmela/11-13-96
X:\new\firmsam\barr\ltrs&rev\40135ap.d
F/T by MM November 20, 1996
Approval Letter

11/25/96

PHARMACIST NOTE:
Dispense with patient leaflet.

Usual Dosage: See package brochure.

Each tablet contains:
Estropipate 3 mg, calculated as sodium estrone sulfate 2.5 mg.

Dispense with a child-resistant closure in a tight, light-resistant container.

Store at controlled room temperature 15°-30°C (59°-86°F).

BARR LABORATORIES, INC.
Pomona, NY 10970

R9-96

BARR LABORATORIES, INC.

Estropipate Tablets, USP 3 mg

Caution: Federal law prohibits dispensing without prescription.

21 Tablets

NDC 0555-0729-38

3 0555-0729-38 9

SAMPLE

Exp. Date:

Lot No.:

PHARMACIST NOTE:
Dispense with patient leaflet.

Usual Dosage: See package brochure.

Each tablet contains:
Estropipate 3 mg, calculated as sodium estrone sulfate 2.5 mg.

Dispense with a child-resistant closure in a tight, light-resistant container.

Store at controlled room temperature 15°-30°C (59°-86°F).

BARR LABORATORIES, INC.
Pomona, NY 10970

R9-96

BARR LABORATORIES, INC.

Estropipate Tablets, USP 3 mg

Caution: Federal law prohibits dispensing without prescription.

100 Tablets

NDC 0555-0729-02

3 0555-0729-02 0

SAMPLE

Exp. Date:

Lot No.:

PHARMACIST NOTE:
Dispense with patient leaflet.

Usual Dosage: See package brochure.

Each tablet contains:
Estropipate 3 mg, calculated as sodium estrone sulfate 2.5 mg.

Dispense with a child-resistant closure in a tight, light-resistant container.

Store at controlled room temperature 15°-30°C (59°-86°F).

BARR LABORATORIES, INC.
Pomona, NY 10970

R9-96

BARR LABORATORIES, INC.

Estropipate Tablets, USP 3 mg

Caution: Federal law prohibits dispensing without prescription.

1000 Tablets

NDC 0555-0729-05

3 0555-0729-05 1

SAMPLE

Exp. Date:

Lot No.:

PHARMACIST NOTE:
Dispense with patient leaflet.

Usual Dosage: See package brochure.

Each tablet contains:
Estropipate 1.5 mg, calculated as sodium estrone sulfate 1.25 mg.

Dispense with a child-resistant closure in a tight, light-resistant container.

Store at controlled room temperature 15°-30°C (59°-86°F).

BARR LABORATORIES, INC.
Pomona, NY 10970

R9-96

BARR LABORATORIES, INC.

Estropipate Tablets, USP 1.5 mg

Caution: Federal law prohibits dispensing without prescription.

21 Tablets

NDC 0555-0728-38

SAMPLE

Exp. Date:

Lot No.:

PHARMACIST NOTE:
Dispense with patient leaflet.

Usual Dosage: See package brochure.

Each tablet contains:
Estropipate 1.5 mg, calculated as sodium estrone sulfate 1.25 mg.

Dispense with a child-resistant closure in a tight, light-resistant container.

Store at controlled room temperature 15°-30°C (59°-86°F).

BARR LABORATORIES, INC.
Pomona, NY 10970

R9-96

BARR LABORATORIES, INC.

Estropipate Tablets, USP 1.5 mg

Caution: Federal law prohibits dispensing without prescription.

100 Tablets

NDC 0555-0728-02

SAMPLE

Exp. Date:

Lot No.:

PHARMACIST NOTE:
Dispense with patient leaflet.

Usual Dosage: See package brochure.

Each tablet contains:
Estropipate 1.5 mg, calculated as sodium estrone sulfate 1.25 mg.

Dispense with a child-resistant closure in a tight, light-resistant container.

Store at controlled room temperature 15°-30°C (59°-86°F).

BARR LABORATORIES, INC.
Pomona, NY 10970

R9-96

BARR LABORATORIES, INC.

Estropipate Tablets, USP 1.5 mg

Caution: Federal law prohibits dispensing without prescription.

1000 Tablets

NDC 0555-0728-05

SAMPLE

Exp. Date:

Lot No.:

PHARMACIST NOTE:
Dispense with patient leaflet.

Usual Dosage: See package brochure.

Each tablet contains:
Estropipate 0.75 mg, calculated as sodium estrone sulfate 0.625 mg.

Dispense with a child-resistant closure in a tight, light-resistant container.

Store at controlled room temperature 15°-30°C (59°-86°F).

BARR LABORATORIES, INC.
Pomona, NY 10970

R9-96

BARR LABORATORIES, INC.

Estropipate Tablets, USP 0.75 mg

Caution: Federal law prohibits dispensing without prescription.

21 Tablets

NDC 0555-0727-38

3 0555-0727-38 5

Exp. Date:

Lot No.:

SAMPLE

PHARMACIST NOTE:
Dispense with patient leaflet.

Usual Dosage: See package brochure.

Each tablet contains:
Estropipate 0.75 mg, calculated as sodium estrone sulfate 0.625 mg.

Dispense with a child-resistant closure in a tight, light-resistant container.

Store at controlled room temperature 15°-30°C (59°-86°F).

BARR LABORATORIES, INC.
Pomona, NY 10970

R9-96

BARR LABORATORIES, INC.

Estropipate Tablets, USP 0.75 mg

Caution: Federal law prohibits dispensing without prescription.

100 Tablets

NDC 0555-0727-02

3 0555-0727-02 6

Exp. Date:

Lot No.:

SAMPLE

PHARMACIST NOTE:
Dispense with patient leaflet.

Usual Dosage: See package brochure.

Each tablet contains:
Estropipate 0.75 mg, calculated as sodium estrone sulfate 0.625 mg.

Dispense with a child-resistant closure in a tight, light-resistant container.

Store at controlled room temperature 15°-30°C (59°-86°F).

BARR LABORATORIES, INC.
Pomona, NY 10970

R9-96

BARR LABORATORIES, INC.

Estropipate Tablets, USP 0.75 mg

Caution: Federal law prohibits dispensing without prescription.

1000 Tablets

NDC 0555-0727-05

3 0555-0727-05 7

Exp. Date:

Lot No.:

SAMPLE

ESTROPIPATE TABLETS, USP

SAMPLE

Revised JUNE 1996
1007270101

WARNINGS:

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA IN POSTMENOPAUSAL WOMEN.

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equi-estrogenic doses.

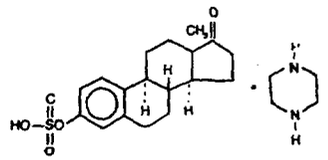
2. ESTROGENS SHOULD NOT BE USE DURING PREGNANCY.

There is no indication for estrogen therapy during pregnancy or during the immediate postpartum period. Estrogens are ineffective for the prevention or treatment of threatened or habitual abortion. Estrogens are not indicated for the prevention of postpartum breast engorgement.

Estrogen therapy during pregnancy is associated with an increased risk of congenital defects in the reproductive organs of the fetus, and possibly other birth defects. Studies of women who received diethylstilbestrol (DES) during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possibly testicular cancer later in life. The 1985 DES Task Force concluded that use of DES during pregnancy is associated with a subsequent increased risk of breast cancer in the mothers, although a causal relationship remains unproven and the observed level of excess risk is similar to that for a number of other breast cancer risk factors.

DESCRIPTION:

Estropipate, (formerly piperazine estrone sulfate), is a natural estrogenic substance prepared from purified crystalline estrone, solubilized as the sulfate and stabilized with piperazine. It is appreciably soluble in water and has almost no odor or taste - properties which are ideally suited for oral administration. The amount of piperazine in Estropipate Tablets is not sufficient to exert a pharmacological action. Its addition ensures solubility, stability, and uniform potency of the estrone sulfate. Chemically estropipate is represented by estra-1,3,5(10)-trien-17-one, 3-(sulfooxy)-, compound with piperazine (1:1). The structural formula may be represented as follows:



$C_{18}H_{22}O_5S \cdot C_4H_{10}N_2$ Molecular Weight: 436.56

Estropipate Tablets are available for oral administration containing 0.75 mg, 1.5 mg or 3 mg estropipate (calculated as sodium estrone sulfate 0.625 mg, 1.25 mg and 2.5 mg, respectively).

Inactive Ingredients: Colloidal silicon dioxide, crospovidone, lactose monohydrate, magnesium stearate, and pregelatinized starch. The 0.75 mg also contains D&C yellow no. 10 aluminum lake and FD&C yellow no. 6 aluminum lake. The 1.5 mg also contains FD&C yellow no. 6 aluminum lake. The 3 mg also contains FD&C blue no. 2 aluminum lake.

CLINICAL PHARMACOLOGY:

Estrogen drug products act by regulating the transcription of a limited number of genes. Estrogens diffuse through cell membranes, distribute themselves throughout the cell, and bind to and activate the nuclear estrogen receptor, a DNA-binding protein which is found in estrogen-responsive tissues. The activated estrogen receptor binds to specific DNA sequences, or hormone-response elements, which enhance the transcription of adjacent genes and in turn lead to the observed effects. Estrogen receptors have been identified in tissues of the reproductive tract, breast, pituitary, hypothalamus, liver, and bone of women.

Estrogens are important in the development and maintenance of the female reproductive system and secondary sex characteristics. By a direct action, they cause growth and development of the uterus, Fallopian tubes, and vagina. With other hormones, such as pituitary hormones and progesterone, they cause enlargement of the breasts through promotion of ductal growth, stromal development, and the accretion of fat. Estrogens are intricately involved with other hormones, especially progesterone, in the processes of the ovulatory menstrual cycle and pregnancy, and affect the release of pituitary gonadotropins. They also contribute to the shaping of the skeleton, maintenance of tone and elasticity of urogenital structures, changes in the epiphyses of the long bones that allow for the pubertal growth spurt and its termination, and pigmentation of the nipples and genitals.

Estrogens occur naturally in several forms. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 micrograms of estradiol daily, depending on the phase of the menstrual cycle. This is converted primarily to estrone, which circulates in roughly equal proportion to estradiol, and to small amounts of estriol. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone—especially in its sulfate ester form—is the most abundant circulating estrogen in postmenopausal women. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than estrone or estriol at the receptor.

Estrogens used in therapy are well absorbed through the skin, mucous membranes, and [illegible] applied for a local action, absorption is usually sufficient to [illegible]

allow for the pubertal growth spurt and its termination, and pigmentation of the nipples and genitals.

Estrogens occur naturally in several forms. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 micrograms of estradiol daily, depending on the phase of the menstrual cycle. This is converted primarily to estrone, which circulates in roughly equal proportion to estradiol, and to small amounts of estriol. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone—especially in its sulfate ester form—is the most abundant circulating estrogen in postmenopausal women. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than estrone or estriol at the receptor.

Estrogens used in therapy are well absorbed through the skin, mucous membranes, and gastrointestinal tract. When applied for a local action, absorption is usually sufficient to cause systemic effects. When conjugated with aryl and alkyl groups for parenteral administration, the rate of absorption of oily preparations is slowed with a prolonged duration of action, such that a single intramuscular injection of estradiol valerate or estradiol cypionate is absorbed over several weeks.

Administered estrogens and their esters are handled within the body essentially the same as the endogenous hormones. Metabolic conversion of estrogens occurs primarily in the liver (first pass effect), but also at local target tissue sites. Complex metabolic processes result in a dynamic equilibrium of circulating conjugated and unconjugated estrogenic forms which are continually interconverted, especially between estrone and estradiol and between esterified and non-esterified forms. Although naturally-occurring estrogens circulate in the blood largely bound to sex hormone-binding globulin and albumin, only unbound estrogens enter target tissue cells. A significant proportion of the circulating estrogen exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogenic species. A certain proportion of the estrogen is excreted into the bile and then reabsorbed from the intestine. During this enterohepatic recirculation, estrogens are desulfated and resulfated and undergo degradation through conversion to less active estrogens (estriol and other estrogens), oxidation to nonestrogenic substances (catecholestrogens, which interact with catecholamine metabolism, especially in the central nervous system), and conjugation with glucuronic acids (which are then rapidly excreted in the urine).

When given orally, naturally-occurring estrogens and their esters are extensively metabolized (first pass effect) and circulate primarily as estrone sulfate, with smaller amounts of other conjugated and unconjugated estrogenic species. This results in limited oral potency. By contrast, synthetic estrogens, such as ethinyl estradiol and the nonsteroidal estrogens, are degraded very slowly in the liver and other tissues, which results in their high intrinsic potency. Estrogen drug products administered by non-oral routes are not subject to first-pass metabolism, but also undergo significant hepatic uptake, metabolism, and enterohepatic recycling.

INDICATIONS AND USAGE:

Estropipate tablets are indicated in the:

1. Treatment of moderate to severe vasomotor symptoms associated with menopause. There is no adequate evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause and they should not be used to treat these conditions.
2. Treatment of vulval and vaginal atrophy.
3. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.
4. Prevention of osteoporosis.

Since estrogen administration is associated with risk, selection of patients should ideally be based on prospective identification of risk factors for developing osteoporosis. Unfortunately, there is no certain way to identify those women who will develop osteoporotic fractures. Most prospective studies of efficacy for this indication have been carried out in white menopausal women, without stratification by other risk factors, and tend to show a universally salutary effect on bone. Thus, patient selection must be individualized based on the balance of risks and benefits. A more favorable risk/benefit ratio exists in a hysterectomized woman because she has no risk of endometrial cancer (see Boxed **WARNINGS**).

Estrogen replacement therapy reduces bone resorption and retards or halts postmenopausal bone loss. Case-control studies have shown an approximately 60 percent reduction in hip and wrist fractures in women whose estrogen replacement was begun within a few years of menopause. Studies also suggest that estrogen reduces the rate of vertebral fractures. Even when started as late as 6 years after menopause, estrogen prevents further loss of bone mass for as long as the treatment is continued. The results of a double-blind, placebo-controlled two-year study have shown that treatment with one tablet of estropipate 0.75 mg daily for 25 days (of a 31-day cycle per month) prevents vertebral bone mass loss in postmenopausal women. When estrogen therapy is discontinued, bone mass declines at a rate comparable to the immediate postmenopausal period. There is no evidence that estrogen replacement therapy restores bone mass to premenopausal levels.

At skeletal maturity there are sex and race differences in both the total amount of bone present and its density, in favor of men and blacks. Thus, women are at higher risk than men because they start with less bone mass and, for several years following natural or induced menopause, the rate of bone mass decline is accelerated. White and Asian women are at higher risk than black women.

Early menopause is one of the strongest predictors for the development of osteoporosis. In addition, other factors affecting the skeleton which are associated with osteoporosis include genetic factors (small build, family history), endocrine factors (nulliparity, thyrotoxicosis, hyperparathyroidism, Cushing's syndrome, hyperprolactinemia, Type I diabetes), lifestyle (cigarette smoking, alcohol abuse, sedentary exercise habits) and nutrition (below average body weight, dietary calcium intake).

The mainstays of prevention and management of osteoporosis are estrogen, an adequate lifetime calcium intake, and exercise. Postmenopausal women absorb dietary calcium less efficiently than premenopausal women and require an average of 1500 mg/day of elemental calcium to remain in neutral calcium balance. By comparison, premenopausal women require about 1000 mg/day and the average calcium intake in the USA is 400-600 mg/day. Therefore, when not contraindicated, calcium supplementation may be helpful.

Weight-bearing exercise and nutrition may be important adjuncts to the prevention and management of osteoporosis. Immobilization and prolonged bed rest produce rapid bone loss, while weight-bearing exercise has been shown both to reduce bone loss and to increase bone mass. The optimal type and amount of physical activity that would prevent osteoporosis have not been established, however in two studies an hour of walking and running exercises twice or three times weekly significantly increased lumbar spine bone mass.

CONTRAINDICATIONS:

Estrogens should not be used in individuals with any of the following conditions:

1. Known or suspected pregnancy (see Boxed **WARNINGS**). Estrogens may cause fetal harm when administered to a pregnant woman.
2. Undiagnosed abnormal genital bleeding.
3. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease.
4. Known or suspected estrogen-dependent neoplasia.
5. Active thrombophlebitis or thromboembolic disorders.

WARNINGS:

Induction of Malignant Neoplasms:

Endometrial Cancer: The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than one year. The greatest risk appears associated with prolonged use—with increased risks of 15 to 24-fold for five to ten years or more. In three studies, persistence of risk was demonstrated for 8 to over 15 years after cessation of estrogen treatment. In one study a significant decrease in the incidence of endometrial cancer occurred six months after estrogen withdrawal. Concurrent progestin therapy may offset this risk but the overall health impact in postmenopausal women is not known (see **PRECAUTIONS**).

Breast Cancer: While the majority of studies have not shown an increased risk of breast cancer in women who have ever used estrogen replacement therapy, some have reported a moderately increased risk (relative risks of 1.3 - 2.0) in those taking higher doses or those taking lower doses for prolonged periods of time, especially in excess of 10 years. Other studies have not shown this relationship.

Congenital Lesions with Malignant Potential: Estrogen therapy during pregnancy is associated with an increased risk of fetal congenital reproductive tract disorders, and possibly other birth defects. Studies of women who received DES during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of [illegible]

diol daily, depending on the phase of the menstrual cycle. This is converted primarily to estrone, which circulates in roughly equal proportion to estradiol, and to small amounts of estriol. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone—especially in its sulfate ester form—is the most abundant circulating estrogen in postmenopausal women. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than estrone or estriol at the receptor.

Estrogens used in therapy are well absorbed through the skin, mucous membranes, and gastrointestinal tract. When applied for a local action, absorption is usually sufficient to cause systemic effects. When conjugated with aryl and alkyl groups for parenteral administration, the rate of absorption of oily preparations is slowed with a prolonged duration of action, such that a single intramuscular injection of estradiol valerate or estradiol cypionate is absorbed over several weeks.

Administered estrogens and their esters are handled within the body essentially the same as the endogenous hormones. Metabolic conversion of estrogens occurs primarily in the liver (first pass effect), but also at local target tissue sites. Complex metabolic processes result in a dynamic equilibrium of circulating conjugated and unconjugated estrogenic forms which are continually interconverted, especially between estrone and estradiol and between esterified and non-esterified forms. Although naturally-occurring estrogens circulate in the blood largely bound to sex hormone-binding globulin and albumin, only unbound estrogens enter target tissue cells. A significant proportion of the circulating estrogen exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogenic species. A certain proportion of the estrogen is excreted into the bile and then reabsorbed from the intestine. During this enterohepatic recirculation, estrogens are desulfated and resulfated and undergo degradation through conversion to less active estrogens (estriol and other estrogens), oxidation to nonestrogenic substances (catecholestrogens, which interact with catecholamine metabolism, especially in the central nervous system), and conjugation with glucuronic acids (which are then rapidly excreted in the urine).

When given orally, naturally-occurring estrogens and their esters are extensively metabolized (first pass effect) and circulate primarily as estrone sulfate, with smaller amounts of other conjugated and unconjugated estrogenic species. This results in limited oral potency. By contrast, synthetic estrogens, such as ethinyl estradiol and the nonsteroidal estrogens, are degraded very slowly in the liver and other tissues, which results in their high intrinsic potency. Estrogen drug products administered by non-oral routes are not subject to first-pass metabolism, but also undergo significant hepatic uptake, metabolism, and enterohepatic recycling.

INDICATIONS AND USAGE:

Estropipate tablets are indicated in the:

1. Treatment of moderate to severe vasomotor symptoms associated with menopause. There is no adequate evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause and they should not be used to treat these conditions.
2. Treatment of vulval and vaginal atrophy.
3. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.
4. Prevention of osteoporosis.

Since estrogen administration is associated with risk, selection of patients should ideally be based on prospective identification of risk factors for developing osteoporosis. Unfortunately, there is no certain way to identify those women who will develop osteoporotic fractures. Most prospective studies of efficacy for this indication have been carried out in white menopausal women, without stratification by other risk factors, and tend to show a universally salutary effect on bone. Thus, patient selection must be individualized based on the balance of risks and benefits. A more favorable risk/benefit ratio exists in a hysterectomized woman because she has no risk of endometrial cancer (see Boxed **WARNINGS**).

Estrogen replacement therapy reduces bone resorption and retards or halts postmenopausal bone loss. Case-control studies have shown an approximately 60 percent reduction in hip and wrist fractures in women whose estrogen replacement was begun within a few years of menopause. Studies also suggest that estrogen reduces the rate of vertebral fractures. Even when started as late as 6 years after menopause, estrogen prevents further loss of bone mass for as long as the treatment is continued. The results of a double-blind, placebo-controlled two-year study have shown that treatment with one tablet of estropipate 0.75 mg daily for 25 days (of a 31-day cycle per month) prevents vertebral bone mass loss in postmenopausal women. When estrogen therapy is discontinued, bone mass declines at a rate comparable to the immediate postmenopausal period. There is no evidence that estrogen replacement therapy restores bone mass to premenopausal levels.

At skeletal maturity there are sex and race differences in both the total amount of bone present and its density, in favor of men and blacks. Thus, women are at higher risk than men because they start with less bone mass and, for several years following natural or induced menopause, the rate of bone mass decline is accelerated. White and Asian women are at higher risk than black women.

Early menopause is one of the strongest predictors for the development of osteoporosis. In addition, other factors affecting the skeleton which are associated with osteoporosis include genetic factors (small build, family history), endocrine factors (multiparity, thyrotoxicosis, hyperparathyroidism, Cushing's syndrome, hyperprolactinemia, Type I diabetes), lifestyle (cigarette smoking, alcohol abuse, sedentary exercise habits) and nutrition (below average body weight, dietary calcium intake).

The mainstays of prevention and management of osteoporosis are estrogen, an adequate lifetime calcium intake, and exercise. Postmenopausal women absorb dietary calcium less efficiently than premenopausal women and require an average of 1500 mg/day of elemental calcium to remain in neutral calcium balance. By comparison, premenopausal women require about 1000 mg/day and the average calcium intake in the USA is 400-600 mg/day. Therefore, when not contraindicated, calcium supplementation may be helpful.

Weight-bearing exercise and nutrition may be important adjuncts to the prevention and management of osteoporosis. Immobilization and prolonged bed rest produce rapid bone loss, while weight-bearing exercise has been shown both to reduce bone loss and to increase bone mass. The optimal type and amount of physical activity that would prevent osteoporosis have not been established, however in two studies an hour of walking and running exercises twice or three times weekly significantly increased lumbar spine bone mass.

CONTRAINDICATIONS:

Estrogens should not be used in individuals with any of the following conditions:

1. Known or suspected pregnancy (see Boxed **WARNINGS**). Estrogens may cause fetal harm when administered to a pregnant woman.
2. Undiagnosed abnormal genital bleeding.
3. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease.
4. Known or suspected estrogen-dependent neoplasia.
5. Active thrombophlebitis or thromboembolic disorders.

WARNINGS:

Induction of Malignant Neoplasms:

Endometrial Cancer: The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than one year. The greatest risk appears associated with prolonged use—with increased risks of 15 to 24-fold for five to ten years or more. In three studies, persistence of risk was demonstrated for 8 to over 15 years after cessation of estrogen treatment. In one study a significant decrease in the incidence of endometrial cancer occurred six months after estrogen withdrawal. Concurrent progestin therapy may offset this risk but the overall health impact in postmenopausal women is not known (see **PRECAUTIONS**).

Breast Cancer: While the majority of studies have not shown an increased risk of breast cancer in women who have ever used estrogen replacement therapy, some have reported a moderately increased risk (relative risks of 1.3 - 2.0) in those taking higher doses or those taking lower doses for prolonged periods of time, especially in excess of 10 years. Other studies have not shown this relationship.

Congenital Lesions with Malignant Potential: Estrogen therapy during pregnancy is associated with an increased risk of fetal congenital reproductive tract disorders, and possibly other birth defects. Studies of women who received DES during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possibly testicular cancer later in life. Although some of these changes are benign, others are precursors of malignancy.

Gallbladder Disease:

Two studies have reported a 2- to 4-fold increase in the risk of gallbladder disease requir-

Congenital Lesions ...

ated with an increased risk of fetal congenital reproductive tract disorders and possibly other birth defects. Studies of women who received DES during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possibly testicular cancer later in life. Although some of these changes are benign, others are precursors of malignancy.

Gallbladder Disease:

Two studies have reported a 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving postmenopausal estrogens.

Cardiovascular Disease:

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis. These risks cannot necessarily be extrapolated from men to women. However, to avoid the theoretical cardiovascular risk to women caused by high estrogen doses, the dose for estrogen replacement therapy should not exceed the lowest effective dose.

Elevated blood pressure:

Occasional blood pressure increases during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens. More often, blood pressure has remained the same or has dropped. One study showed that postmenopausal estrogen users have higher blood pressure than nonusers. Two other studies showed slightly lower blood pressure among estrogen users compared to nonusers. Postmenopausal estrogen use does not increase the risk of stroke. Nonetheless, blood pressure should be monitored at regular intervals with estrogen use.

Hypercalcemia:

Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

PRECAUTIONS:

General:

Addition of a Progestin: Studies of the addition of a progestin for ten or more days of a cycle of estrogen administration have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Morphological and biochemical studies of endometria suggest that 10 to 14 days of progestin are needed to provide maximal maturation of the endometrium and to reduce the likelihood of hyperplastic changes.

There are, however, possible risks which may be associated with the use of progestins in estrogen replacement regimens. These include: (1) adverse effects on lipoprotein metabolism (lowering HDL and raising LDL) which could diminish the purported cardioprotective effect of estrogen therapy (see **PRECAUTIONS** below); (2) impairment of glucose tolerance; and (3) possible enhancement of mitotic activity in breast epithelial tissue, although few epidemiological data are available to address this point (see **PRECAUTIONS** below).

The choice of progestin, its dose, and its regimen may be important in minimizing these adverse effects, but these issues remain to be clarified.

Cardiovascular Risk: A causal relationship between estrogen replacement therapy and reduction of cardiovascular disease in postmenopausal women has not been proven. Furthermore, the effect of added progestins on this putative benefit is not yet known.

In recent years many published studies have suggested that there may be a cause-effect relationship between postmenopausal oral estrogen replacement therapy without added progestins and a decrease in cardiovascular disease in women. Although most of the observational studies which assessed this statistical association have reported a 20% to 50% reduction in coronary heart disease risk and associated mortality in estrogen takers, the following should be considered when interpreting these reports:

(1) Because only one of these studies was randomized and it was too small to yield statistically significant results, all relevant studies were subject to selection bias. Thus, the apparently reduced risk of coronary artery disease cannot be attributed with certainty to estrogen replacement therapy. It may instead have been caused by life-style and medical characteristics of the women studied with the result that healthier women were selected for estrogen therapy. In general, treated women were of higher socioeconomic and educational status, more slender, more physically active, more likely to have undergone surgical menopause, and less likely to have diabetes than the untreated women. Although some studies attempted to control for these selection factors, it is common for properly designed randomized trials to fail to confirm benefits suggested by less rigorous study designs. Thus, ongoing and future large-scale randomized trials may fail to confirm this apparent benefit.

(2) Current medical practice often includes the use of concomitant progestin therapy in women with intact uteri (see **PRECAUTIONS** and **WARNINGS**). While the effects of added progestins on the risk of ischemic heart disease are not known, all available progestins reverse at least some of the favorable effects of estrogens on HDL and LDL levels.

(3) While the effects of added progestins on the risk of breast cancer are also unknown, available epidemiological evidence suggests that progestins do not reduce, and may enhance, the moderately increased breast cancer incidence that has been reported with prolonged estrogen replacement therapy (see **WARNINGS** above).

Because relatively long-term use of estrogens by a woman with a uterus has been shown to induce endometrial cancer, physicians often recommend that women who are deemed candidates for hormone replacement should take progestins as well as estrogens. When considering prescribing concomitant estrogens and progestins for hormone replacement therapy, physicians and patients are advised to carefully weigh the potential benefits and risks of the added progestin. Large-scale randomized, placebo-controlled, prospective clinical trials are required to clarify these issues.

Physical Examination: A complete medical and family history should be taken prior to the initiation of any estrogen therapy. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than one year without reexamining the patient.

Hypercoagulability: Some studies have shown that women taking estrogen replacement therapy have hypercoagulability, primarily related to decreased antithrombin activity. This effect appears dose- and duration-dependent and is less pronounced than that associated with oral contraceptive use. Also, postmenopausal women tend to have increased coagulation parameters at baseline compared to premenopausal women. There is some suggestion that low dose postmenopausal mestranol may increase the risk of thromboembolism, although the majority of studies (of primarily conjugated estrogens users) report no such increase. There is insufficient information on hypercoagulability in women who have had previous thromboembolic disease.

Familial Hyperlipoproteinemia: Estrogen therapy may be associated with massive elevations of plasma triglycerides leading to pancreatitis and other complications in patients with familial defects of lipoprotein metabolism.

Fluid Retention: Because estrogens may cause some degree of fluid retention, conditions which might be exacerbated by this factor, such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.

Uterine Bleeding and Mastodynia: Certain patients may develop undesirable manifestations of estrogenic stimulation, such as abnormal uterine bleeding and mastodynia.

Impaired Liver Function: Estrogens may be poorly metabolized in patients with impaired liver function and should be administered with caution.

Information for the Patient:

See text of Patient Package Leaflet below.

Laboratory Tests:

Estrogen administration should generally be guided by clinical response at the smallest dose, rather than laboratory monitoring, for relief of symptoms for those indications in which symptoms are observable. For prevention and treatment of osteoporosis, however, see **DOSAGE AND ADMINISTRATION** section.

Drug/Laboratory Test Interactions:

Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered.

Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin sub-

... antiplasmin)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 40-135 **SPONSOR:** Barr Labortaories
DOSAGE FORM: Estropipate tablets
STRENGTHS(s): 0.75 mg, 1.5 mg and 3 mg.
TYPE OF STUDY: Single dose fasting study.
STUDY SITE:

STUDY SUMMARY: A fasting bioequivalence study was conducted in 26 healthy *postmenopausal female* volunteers comparing Barr's estropipate 3 mg tablets with Abbot Laboratories' Ogen^R 3 mg tablet. The 90% confidence intervals for the log-transformed AUC, AUC_{inf} and C_{max} data were within the acceptable range of 80-125%. In addition, the analysis of variance revealed no formulation differences or sequence effects for these three parameters. This study demonstrates that Barr's estropipate 3 mg tablet is bioequivalent to the reference product, Ogen^R 3 mg tablet, manufactured by Abbot Laboratories. waivers for the 0.75mg and 1.5mg tablets are granted.

DISSOLUTION: The results of *in vitro* dissolution testing indicated that greater than of the labeled amount of estropipate in the test product was dissolved in 45 minutes. The dissolution testing meets USP specifications.

PRIMARY REVIEWER: Gur J.P. Singh, Ph.D. **BRANCH:** II

INITIAL: DATE 4-12-96

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for **BRANCH CHIEF:** Rabindra N. Patnaik, Ph.D. **BRANCH:** II

INITIAL: DATE 4/12/96

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Keith Chan, Ph.D.

INITIAL: DATE 4/12/96

DIRECTOR, OFFICE OF GENERIC DRUGS: Roger L. Williams, M.D.

INITIAL: Not first seen DATE

AUG 8 1995

Estropipate
Tablet, 3 mg,
ANDA # 40-135
Reviewer: Gur J.P. Singh
File #40135SD.295

Barr Laboratories.
2 Quaker Road
Northvale, NJ 07647
Submission Date:
February 9, 1995

Review of a fasting bioequivalence study and dissolution data

The sponsor has submitted this ANDA on its estropipate 3 mg tablets. This application contains data from a single dose study conducted under fasting conditions and *in vitro* dissolution data. A preliminary review of this application has revealed deficiencies related to the analytical methodology. Therefore, a complete review of this application has been put on hold till the sponsor provides information to resolve the following deficiencies.

DEFICIENCIES:

1.

2.

3.

4. The sponsor should provide evidence for linearity of all calibration curves used for calculation of plasma concentration values of estrone and estrone sulfate.

5. In the analytical section (pp 1024), the sponsor states that "extracted samples from two subjects (a total of six periods)" were analyzed at the same time. This study was conducted as a two period two-way cross over study, and this design allows four period data for two subjects, instead of the six periods mentioned in this application. The sponsor should explain this discrepancy.

RECOMMENDATIONS

1. The *in-vivo* bioequivalence study conducted under fasting condition by Barr Laboratories on its estropipate 3 mg tablet, lot #4R72903, comparing it to the reference product Ogen^{R} 3 mg tablet, lot #73820AA21, manufactured by Abbot, has been found to be incomplete due to deficiencies #1-5.

2. The *in vitro* dissolution testing conducted by Barr Laboratories on its estropipate 3 mg tablets, is acknowledged. Recommendation for *in vitro* dissolution testing will be made on acceptance of the *in vivo* bioequivalence study.

5. From the bioequivalence point of view, the firm has not met the requirements for *in vivo* bioequivalence and *in vitro* dissolution.

Gur J.P. Singh, Ph.D.
Review Branch II, Division of Bioequivalence.

RD INITIALLED RPatnaik
RD INITIALLED RPatnaik 7/28/95

CONCUR: _____ DATE: 8/8/95

Keith Chan, Ph.D.
Director, Division of Bioequivalence.

GJPSINGH/ 7/27/95/40135SD.295
cc: ANDA # 40135 (original, duplicate), HFD-630 (OGD) HFC-130 (Jallen), HFD-600 (Hare), HFD-344 (CVishwanathan), HFD-655 (Patnaik, Singh), Drug file, Division file.

ANDA 40-135

APR - 9 1996

Barr Laboratories, Inc.
Attention: Herbert G. Luther, Ph.D.
2 Quaker Road
P.O. BOX 2900
Pomona NY 10970-0519

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Estropipate Tablets USP, 3 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution should be conducted in 900 mL of water using USP 23 apparatus II (paddles) at 75 rpm. The dissolution testing should meet the following specifications.

   > Not less than of the labeled amount of estropipate is dissolved from the dosage form in 60 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APR 4 1996

Estropipate

Tablets, 0.75 mg, 1.5 mg and 3 mg.
ANDA # 40-135
Reviewer: Gur J.P. Singh
File #40135SDW.O96

Barr Laboratories.

2 Quaker Road
Northvale, NJ 07647
Submission Dates:
February 9, 1995
October 24, 1995
February 7, 1996

Review of a fasting bioequivalence study, dissolution data and a waiver request

Introduction

Estropipate is an estrogenic substance prepared from purified crystalline estrone, solubilized as estrone sulfate and stabilized with piperazine. The oral estropipate is prescribed for the treatment of estrogen deficiency. The brand name product, Ogen^{R} (Abbot Laboratories), is available as 0.75, 1.5, 3.0 and 6.0 mg oral tablets.

Estrone sulfate is rapidly and completely absorbed from the GI tract with peak plasma concentration occurring approximately 4-5 hours after oral administration. The drug is highly bound to serum albumin. Its elimination half life is in the range of 12-20 hours.

Background

The sponsor submitted a single dose fasting bioequivalence study on February 9, 1995 comparing its estropipate 3 mg tablets with the reference product, Ogen^{R} 3 mg tablet manufactured by Abbot Laboratories. Preliminary review of this application was completed on August 8, 1995 (Reviewer: GJP Singh), and the study was found to be incomplete due to variety of deficiencies related to the analytical method validation. The sponsor was informed of these deficiencies in the Division of Bioequivalence letter of August 22, 1995.

In its study amendment of October 24, 1995, the sponsor has submitted satisfactory response to all deficiencies listed in the August 22, 1995 letter. The following review of the bioequivalence study is based on all data submitted hitherto.

Fasting Bioequivalence Study

OBJECTIVE: The purpose of this study was to establish bioequivalence of Barr Laboratories' estropipate 3 mg tablets to Abbot's Ogen^{R} 3 mg tablets in a single dose, two-treatment, two-period, crossover design with a washout period of seven days between two dosing days.

STUDY SITE, INVESTIGATORS AND DATES:

Clinical and Analytical site: The clinical study was conducted at and sample analyses were conducted at

Medical Director:
Analytical Director

Study Protocol: Protocol (#P94-050, June 30, 1994, pp 85-115, vol 1.1) used for this study was approved by the

Dosing Dates: Group I: Phase I - July 9, Phase 2 - July 16, 1994
Group II: Phase I - July 30, Phase 2 - August 6, 1994

Analytical Dates: July 7 - August 9, 1994

SUBJECT SELECTION:

Twenty eight (28) healthy *postmenopausal female* volunteers were enrolled for this study. The average age and weight of these volunteers were 52.5 years (range = 45-57) and 68.6 kg (range =58-89), respectively. The protocol called for 24 female volunteers with four alternatives. However, a total of 26 subjects were dosed with the test formulations. Subjects were dosed in two groups due to recruitment difficulties. All volunteers were within 15% of their ideal body weight. Subjects who entered this study were selected on the basis of their acceptable medical history, physical examination (including breast examination, gynecological examination with PAP smear) and normal clinical laboratory tests for hematopoietic, hepatic and renal functions.

Subjects were excluded from this study based on the following criteria:

* Cardiovascular, hepatic, renal, neurological, hematological, or gastrointestinal disease.
* Recent history of alcohol/drug abuse.
* Presence of estrogen dependent neoplasia, postmenopausal uterine bleeding, or documented endometrial hyperplasia.
* History or presence of clinically significant fibrocystic breast disease or breast nodules or breast cancer.

* Presence of a condition known to interfere with absorption. distribution , metabolism and excretion of drugs.
* Hypersensitivity to estropipate and related products.
* Current use of tobacco.
* Treatment within 30 days with drug(s) know to effect hepatic enzyme induction..
* Donation of blood in excess of 150 mL over the preceding 30 weeks.
* Treatment with an investigation new drug 30 days prior to the study start.

STUDY DESIGN: The clinical study was conducted as a single dose randomized, two treatment, two-period crossover evaluation with the following subject randomization:

TREATMENT-SEQUENCE		SUBJECT NUMBER
Phase I	*Phase II*	
A	B	101,106, 107, 110, 111, 112, 113, 116, 120, 123, 124, 125, 126, 127
B	A	102, 103, 104, 105, 108, 109, 114, 115, 117, 118, 119, 121, 122, 128

where:

A: Estropipate tablets 1x3 mg, Barr Laboratories, (lot #4R72903, Lot Size

B: Ogen^{R} tablets 1x3 mg, Abbot (Lot # 73-820-AA-21, Lot Size - Commercial lot, Expiry Date - March 1. 1995).

DOSING AND MEALS:

After an overnight (10 hours) fast, each drug was given orally with 240 mL of water. No fluid except that given with drug administration was allowed until 2 hours after dosing. Four hours after drug administration waster was allowed *ad libitum*. Subjects were served standard meals (pp 1204, vol 1.3) free of xanthine containing food or beverages.

SAMPLE COLLECTION AND STORAGE:

Serial blood samples were collected in EDTA containing tubes at predose -48, -24, -0.25, 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, 30, 36, 48 and 72 hours after dosing. Blood samples were centrifuged within 15 minutes of venipuncture, and plasma separated and stored below at approximately -20°C until shipment for analysis. At the completion of each study period. the samples were shipped frozen (in dry ice) to the analytical laboratory.

ANALYTICAL PROCEDURE (Not to be released under FOI):

PHARMACOKINETIC DATA ANALYSIS: Area under the plasma concentration curve from zero to the last measurable concentration (AUC) was calculated using the trapezoidal integration. Extrapolation of the AUC from the last measured concentration to infinity to yield AUC_{inf} was accomplished by addition of the value obtained by dividing this concentration with the elimination rate constant as calculated for each curve. The estrone and estrone sulfate AUC and AUC_{inf} values for each subject were calculated using the raw data and the baseline corrected data. For this correction, the baseline values at three sampling times (-48, -24 and -0.25 hours) prior to dosing were averaged and the average value was used for correction. Other pharmacokinetic parameters determined include C_{max}, T_{max}, elimination $t_{1/2}$ and K_{el}. Statistical analyses of pharmacokinetic data were performed using SAS version 6.06 (SAS Institute Inc, Cary, NC). The analysis of variance with subjects, periods and drugs, group and group*treatment as factors and sequence as between subject factor was applied to estropipate bioavailability parameters and its plasma concentrations at each sampling time point. Statistical analyses of pharmacokinetic data were conducted using the t-test method to determine , at $\alpha = 0.05$ and $\beta = 0.20$, differences between estropipate formulations in AUC, AUC_{inf} and C_{max}.

MISCELLANEOUS:

INSTITUTIONAL REVIEW BOARD: The protocol and bioequivaience study were approved by the

CONSENT FORM: A copy of the volunteer informed consent form used in this study is given on page 1182 (vol 1.3).

RESULTS AND DISCUSSION:

CLINICAL STUDY CONDUCT: All 26 subjects dosed in this study completed the cross over evaluation. Based on the protocol, the firm has used pharmacokinetic data for 24 subjects for bioequivalence determination. In this study, six (Test: 2, Reference: 4) clinical complaints were registered (pp 1155, vol 1.3). Among these events headache (Test: 1, Reference: 3), and nausea (Reference: 1) were considered to be probably related to the test drug. Protocol deviation related to intake of prescription and non-prescription medication were reported in three subjects (pp 1183). These deviations were considered not to impact study integrity.

PHARMACOKINETIC PROFILE: Following the administration of the test and reference products, varying plasma levels of estrone sulfate and the unconjugated estrone were detected, with estrone sulfate levels being greater than those of estrone. Therefore, for determination of bioequivalence, both estrone sulfate and estrone data are reviewed hereafter.

Plasma concentrations of estrone sulfate and estrone for various subjects are given on pages 176-187 (vol 1.1). In this data set several values (Estrone sulfate data 12, estrone data - 2 values) are missing, and these should not affect bioequivalence comparisons. Figures showing individual subject plasma concentration profiles of estrone sulfate and estrone are given on pages 240-289 and 318 - 367 (vol 1.1).

Estrone Sulfate:

The reviewer has performed spot-check calculations to determine the accuracy of the AUC and AUC_{inf} values reported by the firm. The results of these calculations, given below, employing the test product data indicate good agreement between reviewer's calculations and the data reported by the firm.

Subject #	Reviewer(A)		Sponsor (B)		A/B	
	AUC	AUC_{inf}	AUC	AUC_{inf}	AUC	AUC_{inf}
101	570749	598666	570933	598850	0.999	0.999
104	381703	417406	381619	419627	1.000	0.995
119	344879	385029	344827	384977	1.000	1.000
122	392184	438764	392085	438718	1.000	1.000

The AUC/AUCinf ratios for the test and reference products are given in table 3. These data indicate that 97% of all AUC values were within 80-100% of the corresponding AUC_{inf} values. The regression analysis used for calculation of Kel values used for calculation of AUC_{inf} are indicative of r^2 values of 0.84 or above for at least 97% of all determinations. The foregoing data indicate acceptable accuracy in calculations of AUC and AUC_{inf} values.

Plasma concentration profiles of estrone sulfate are summarized in table 1. These data indicate that the test product's plasma levels were within $\pm 20\%$ of those of the reference product at all sampling time points.

Based on parametric values calculated using the uncorrected data, both the test and reference drug products were readily absorbed with T_{max} values of 5.0 and 4.9 hours, respectively (Table 2). The test product had an AUC of 437568 pg/mL*hr and C_{max} of 37525 pg/mL which were 1% and 2% higher than the reference product's respective values. Test product's AUC_{inf} value (462609 pg/mL*hr) was 1% lower than that of the reference product. The difference in the bioavailability of the test and reference products remained similar based on parametric values calculated from baseline-corrected data (Table 2)

The recruitment of subjects in two groups dosed at different times warranted statistical analyses of group*treatment interactions. Based in the ANOVA performed by the reviewer using uncorrected and baseline-corrected data, there were no such interactions (based on *p* values of ≤ 0.1) for the AUC, AUC_{inf} and C_{max} data. Therefore parametric data from two groups was combined for calculation of 90% confidence intervals.

Based on reviewer's calculations using the log transformed uncorrected data, the 90% confidence intervals for AUC, AUC_{inf} and C_{max} data were in the range of 93.77-108.18%, 92.31-105.93% and 92.78 112.69%, respectively (Table 2). For the AUC, AUC_{inf} and C_{max} values based on the baseline corrected data, the 90% confidence intervals were in the range of 93.63-109.24%, 92.07-107.23% and 92.68-112.95%, respectively. In addition, for either the uncorrected or the baseline corrected AUC, AUC_{inf} and C_{max} data, statistical analysis showed no significant period or sequence effect.

Table 3A and 3B show individual subject's parametric data based on uncorrected and baseline corrected plasma concentrations, respectively. When the mean of ratios of individual subject's AUC, AUC_{inf} and C_{max} (Table 3), is compared with respective ratios means (table 2), relative bioavailability of the test and the reference products remains similar.

Estrone:

Plasma concentration profiles of estrone are summarized in table 4. Like the estrone sulfate data, these data also indicate that the test product's plasma levels were within $\pm 20\%$ of those of the reference product at all sampling time points.

Estrone parametric data are shown in Table 5. Based on the uncorrected data, test product's AUC was 2% higher, and its AUC_{inf} was 7% lower than that of the reference product. Estrone C_{max} values were similar following administration of both formulations.

Based on reviewer's calculations using the log transformed uncorrected data, the 90% confidence intervals for AUC, AUC_{inf} and C_{max} data were in the range of 94.4.68 - 108.09%, 83.05-102.52% and 93.11-106.68%, respectively (Table 5). For the AUC, AUC_{inf} and C_{max} values based on the baseline corrected data, the 90% confidence intervals were in the range of 94.87-112.68%, 84.78-107.23% and 93.28-107.50%, respectively. In addition, for either the

uncorrected or the baseline corrected AUC, AUC_{inf} and C_{max} data. statistical analysis showed no significant period or sequence effect.

As mentioned above, recruitment of subjects in two groups dosed at different times warranted statistical analyses of group*treatment interactions. Based in the ANOVA performed by the reviewer using uncorrected and baseline corrected data, there were no such interactions (based on p values of ≤ 0.1) for the AUC_{inf} and C_{max} data. However, significant group*treatment interaction was observed for the log-transformed AUC data ($p = 0.018$ and 0.019 for uncorrected and baseline corrected AUC, respectively). Therefore data from group A (subject #101-107) and group B (subjects 101 -127) were analyzed separately. The results of these analyses given in table 5 show that the 90% confidence intervals for group B were in the acceptable range of 80-125%. However for group A these intervals were out of the acceptable range.

The reviewer considers that the 90% confidence intervals calculated on combined estrone parametric data from groups A and B should be used to establish bioequivalence. instead of the 90% confidence intervals separately calculated for each group. This is because:

i subjects were enrolled in two groups because of recruitment difficulties; these groups are similar with respect to subject demographics (pp 1192, vol 1.3),

ii failure of the Group-A parametric data to meet the 80 - 125% confidence limits is mainly due to small number of subjects enrolled in this group (only 7 subjects),

iii compared with estrone sulfate the contribution of estrone to bioavailabilty comparisons (thus bioequivalence evaluation) is very small because its plasma levels are < 5% of that of estrone suifate. and

iii the group*treatment interactions were detected only for the AUC. and not for the AUC_{inf} and C_{max} data.

Therefore, based on the parametric data for estrone sulfate and estrone. the rate and extent of absorption of the test product is similar to that of the reference product. and these products are bioequivalent.

In Vitro Dissolution Testing

The firm has submitted dissolution data for its estropipate 3 mg tablets and the reference product, Ogen® 3 mg tablet (pp 1998-2000. vol 1.4). Furthermore. in its February 7. 1996 amendment the sponsor submitted dissolution data for its estropipate 0.75 mg and 1.5 mg tablets. and the corresponding strengths of the innovator product. Dissolution of 12 tablets was tested in 900 mL of water using USP XXII apparatus II (paddles) at 75 rpm. The results of *in vitro* dissolution testing (Table 7) indicate that

greater than (Q) of estropipate was dissolved from the test products within 60 minutes. Dissolution testing meets USP specifications. Lot number for estropipate 3 mg tablets used for *in vitro* dissolution testing were identical to those used for *in vivo* bioequivalence studies.

Waiver Request

In the February 7, 1996 amendment, the firm has submitted a request for the waiver of *in vivo* bioequivalence requirements for its estropipate 0.75 mg and 1.5 tablets. It has met requirements of *in vivo* bioequivalence and *in vitro* dissolution testing on its estropipate 3 mg tablets. It has also demonstrated that the compositions of its estropipate 0.75 mg and 1.5 mg estropipate tablets are proportional to that of its estropipate 3 mg tablet (see below), which underwent bioequivalence testing. The dissolution testing on estropipate 0.75 mg and 1.5 mg tablets also meets USP specifications. Therefore, the waiver of *in vivo* bioequivalence requirements for the estropipate 0.75 mg and 1.5 mg tablets may be granted.

Composition (Not to be released under FOI)

Ingredient	mg/Tablet		
	3 mg	1.5 m	0.75 mg
Estropipate, USP	3.15*	1.575*	0.788*
FD&C Blue #2 Aluminum Lake HT			
FD&C Yellow #6 Aluminum Lake HT			
D&C Yellow #10 Aluminum Lake HT			
Pregelatinized Starch, NF (Starch 1500)			
Crospovidon, NF			
Lactose Monohydrate, NF			
Colloidal Silicon Dioxide, NF			
Magnesium Stearate, NF			
Total Weight	*220.00*	*220.00*	*220.00*

** The USP specification for the potency of estropipate in tablets is 90-110% of the labeled amount.*

Comments

This firm has conducted a fasting bioequivalence study on its estropipate 3 mg tablet and the reference drug product, Ogen® 3 mg tablet. The reviewer's comments are as follows:

1. Twenty six (26) subjects were dosed in this study, and all these subjects completed the crossover evaluation. Based on the protocol, the firm has used pharmacokinetic data for 24 subjects for bioequivalence determination. In this study, six (Test: 2, Reference: 4) clinical complaints were registered. Among these events headache (Test: 1, Reference: 3), and nausea (Reference: 1) were considered to be probably related to the test drug.

2. Bioequivalence comparison were based on plasma levels of estrone sulfate and free estrone. Based on reviewer's calculations, the AUC, AUC_{inf} and Cmax 90% confidence intervals for both chemical moieties were within the acceptable limit of 80-125%. In addition, there were no statistically significant treatment, period or sequence effects for AUC and AUC_{inf} and C_{max} data.

3. The results of this study demonstrate that under fasting conditions, Barr Laboratories' estropipate 3 mg tablet is bioequivalent to the reference product, Ogen® 3 mg tablet.

4. By conducting *in vitro* dissolution testing on its estropipate 0.75 mg, 1.5 mg and 3 mg tablets, according to the USP specifications, the firm has demonstrated that greater than of the drug is dissolved in 60 minutes. The lots of the 3 mg strength of test and reference products employed in the *in vitro* dissolution testing were identical to those used for the *in vivo* bioequivalence study. The *in vitro* dissolution data for the test product are acceptable.

5. The firm has met requirements of *in vivo* bioequivalence and *in vitro* dissolution testing on its estropipate 3 mg tablets. It has also demonstrated that the compositions of its estropipate 0.75 mg and 1.5 mg tablets are proportional to that of its 3 mg estropipate tablets, which underwent bioequivalence testing. The dissolution testing on these products meets USP specifications. Therefore, the request for the waiver of *in vivo* bioequivalence requirements for estropipate 0.75 mg and 1.5 mg tablets may be granted.

F. Recommendations

1. The *in-vivo* bioequivalence study conducted under fasting condition by Barr Laboratories on its estropipate 3 mg tablet, lot #4R72903, comparing it to the reference product Ogen® 3 mg tablet, lot #73820AA21, manufactured by Abbot, has been found to be acceptable to the Division of Bioequivalence. The study demonstrates that under fasting conditions, Barr Laboratories' estropipate 3 mg tablets are bioequivalent to Ogen® 3 mg tablets, manufactured by Abbot.

2. The *in vitro* dissolution testing conducted by Barr Laboratories on its estropipate 0.75 mg, 1.5 mg and 3 mg tablets, lot #PD 4R72732, 4R72833 and 4R72903 respectively, is acceptable. The firm has conducted an acceptable single dose *in vivo* bioequivalence study under fasting conditions comparing the 3 mg tablet of the test product with the 3 mg tablet of the reference product, Ogen[R], manufactured by Abbot Laboratories. The formulations for estropipate 0.75 mg and 1.5 mg tablets are proportionally similar to the 3 mg tablet of the test product which underwent bioequivalence testing. The waivers of *in vivo* bioequivalence study requirements for 0.75 mg and 1.5 mg tablets of the test product are granted. The 0.75 mg and 1.5 mg tablets of the test product are therefore deemed bioequivalent to the 0.75 mg and 1.5 mg tablets of the reference product, Ogen[R], manufactured by Abbot Laboratories.

3. The dissolution testing should be incorporated into firm's manufacturing and stability programs. The dissolution should be conducted in 900 mL of water using USP XXII apparatus II (paddles) at 75 rpm. The dissolution testing should meet the following specifications.

   Not less than of the labeled amount of estropipate is dissolved from the dosage form in 60 minutes.

5. From the bioequivalence point of view, the firm has met the requirements for *in vivo* bioequivalence and *in vitro* dissolution testing.

Gur J.P. Singh, Ph.D.
Review Branch II, Division of Bioequivalence.

RD INITIALLED RPatnaik
FT INITIALLED RPatnaik 4/1/96

CONCUR: _____ DATE: 4/4/96
Keith Chan, Ph.D.
Director, Division of Bioequivalence.

GJP SINGH/3/30/96/40135SDW.095
cc: ANDA # 40135 (original, duplicate), HFD-630 (OGD) HFC-130 (Jallen), HFD-600 (Hare), HFD-344 (CVishwanathan), HFD-655 (Patnaik, Singh), Drug file, Division file.

Table 1: Estrone sulfate plasma concentration for the test and reference products (ANDA #40-135, Fasting study)

Time	TEST		REF		TEST/REF
(hr)	CONC	%CV	CONC	%CV	
-48	475	52	532	38	0.89
-24	510	41	488	30	1.04
-0.25	563	53	584	51	0.96
1	11847	129	12224	132	0.97
2	19923	99	16120	88	1.24
3	23524	87	22253	77	1.06
3.5	28463	67	26246	58	1.08
4	28904	59	29508	64	0.98
4.5	30938	55	30161	60	1.03
5	31475	50	30800	53	1.02
5.5	30478	49	32741	54	0.93
6	26854	53	28296	53	0.95
7	24288	48	24077	49	1.01
8	22291	55	21167	52	1.05
10	14252	54	14380	68	0.99
12	11698	64	11542	57	1.01
16	7691	41	8023	50	0.96
24	4923	49	5163	47	0.95
30	3760	49	3960	61	0.95
36	2957	65	3071	57	0.96
48	1816	55	1821	49	1.00
60	1197	51	1173	35	1.02
72	823	44	876	40	0.94

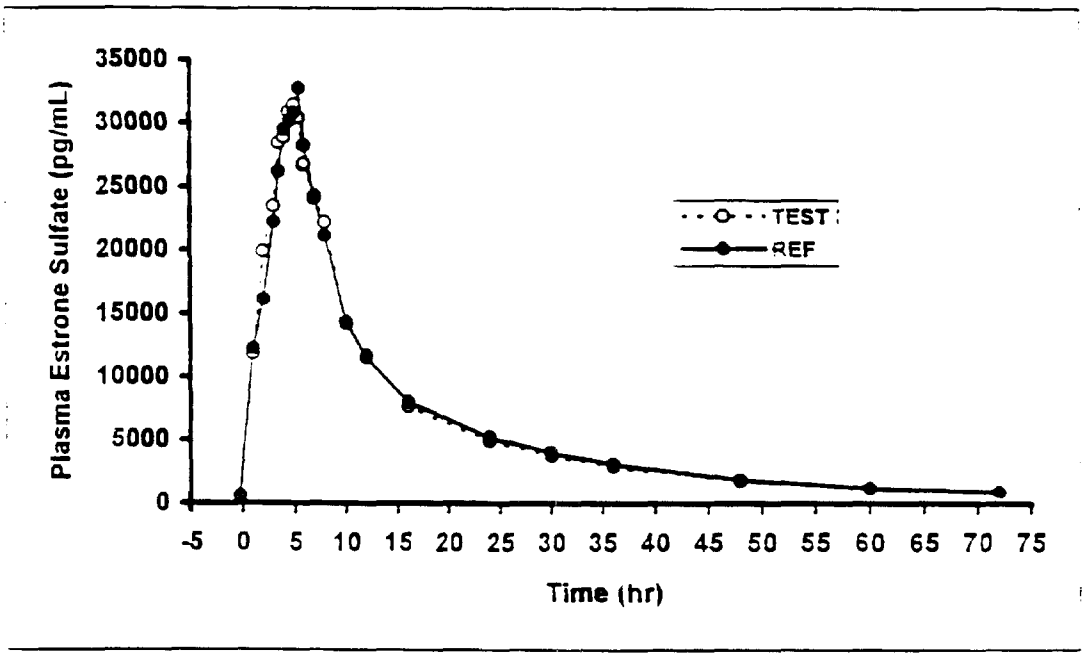

TABLE 2: ESTRONE SULFATE Parametric data, ANDA #40-135, Fasting study

PARAMETER	TEST		REF		TEST/REF	90% CI*	
	Mean	%CV	Mean	%CV			
Based on uncorrected data							
AUC (pg/mL*hr)	437568	53	433728	34	1.01	93.77 -	108.18
AUCinf (pg/mL*hr)	462609	50	465788	35	0.99	92.31 -	105.93
Cmax (pg/mL)	37525	51	36921	37	1.02	92.78 -	112.69
Tmax (hr.)	5.0	23	4.9	18	1.02		
kel (1/hr)	0.035	20	0.034	32	1.03		
t1/2 (hr)	20.35	27	22.62	86	0.90		
Based on data corrected for baseline values							
AUC (pg/mL*hr)	399947	55	396054	55	1.01	93.63 -	109.24
AUCinf (pg/mL*hr)	409886	54	411528	54	1.00	92.07 -	107.38
Cmax (pg/mL)	36998	51	36387	50	1.02	92.68 -	112.95

**** 90% CI are based on ANOVA performed by reviewer using the log transformed parametric data***

TABLE 3A: ESTRONE SULFATE parametric data based on plasma concentrations *not* corrected for baseline values. ANDA #40-135, Fasting study

	TEST							REF							AUC/ AUCinf		TEST/ REF		
SUBJ	BL	AUC	AUCinf	Cmax	Tmax	kel	T1/2	BL	AUC	AUCinf	Cmax	Tmax	kel	T1/2	TEST	REF	AUC	AUCinf	Cmax
101		570933	598850	48200	4.5	0.0345	20.09		478911	528805	31200	5.5	0.0283	24.53	0.95	0.91	1.19	1.13	1.54
102		373771	387270	36000	3.5	0.0349	19.87		364876	383147	37400	4.0	0.0349	19.88	0.97	0.95	1.02	1.01	0.96
103		394777	419627	27600	4.5	0.0389	17.83		339456	374399	25000	4.5	0.0281	24.66	0.94	0.91	1.16	1.12	1.10
104		381619	417322	39300	5.5	0.0370	18.75		723947	753563	67000	5.5	0.0432	16.04	0.91	0.96	0.53	0.55	0.59
105		233885	242628	21100	6.0	0.0337	20.54		242110	254611	33900	4.0	0.0284	24.41	0.96	0.95	0.97	0.95	0.62
106		420257	448060	23100	6.0	0.0374	18.53		413046	443107	27100	6.0	0.0416	16.67	0.94	0.93	1.02	1.01	0.85
107		1361750	1386089	107000	3.0	0.0493	14.06		1339475	1373882	102000	4.0	0.0546	12.69	0.98	0.97	1.02	1.01	1.05
108		279532	313170	32500	3.5	0.0212	32.75		398260	417116	38500	4.0	0.0315	22.00	0.89	0.95	0.70	0.75	0.84
109		421275	447682	30400	5.5	0.0371	18.66		410011	435020	32200	5.0	0.0315	21.97	0.94	0.94	1.03	1.03	0.94
110		281078	287496	39500	4.0	0.0366	18.93		311797	321295	52100	1.0	0.0435	15.94	0.98	0.97	0.90	0.89	0.76
111		213636	222775	28900	4.5	0.0345	20.11		234361	244256	33000	3.5	0.0336	20.66	0.96	0.96	0.91	0.91	0.88
112		311082	324423	24900	6.0	0.0378	18.35		271798	366402	30100	5.5	0.0130	53.31	0.96	0.74	1.14	0.89	0.83
115		512424	532369	51000	5.5	0.0457	15.16		362033	386777	29600	4.5	0.0359	19.31	0.96	0.94	1.42	1.38	1.72
116		353899	366189	29400	7.0	0.0457	15.16		343035	355730	31400	5.5	0.0461	15.04	0.97	0.96	1.03	1.03	0.94
117		367067	386677	23000	5.0	0.0416	16.66		331132	346182	22100	5.5	0.0365	19.00	0.95	0.96	1.11	1.12	1.04
118		502468	531505	43900	5.0	0.0365	18.99		474830	499771	30100	5.0	0.0401	17.29	0.95	0.95	1.06	1.06	1.46
119		344827	384977	36100	4.5	0.0182	38.12		418632	540987	33400	5.0	0.0137	50.48	0.90	0.77	0.82	0.71	1.08
120		588970	603998	63800	3.5	0.0447	15.50		566534	584133	61100	6.0	0.0375	18.48	0.98	0.97	1.04	1.03	1.04
121		451082	493854	27200	8.0	0.0299	23.16		456790	497825	28100	5.0	0.0292	23.70	0.91	0.92	0.99	0.99	0.97
122		392085	438718	28800	5.0	0.0255	27.16		436364	461783	37400	5.0	0.0388	17.85	0.89	0.94	0.90	0.95	0.77
124		379629	407670	27100	5.5	0.0343	20.23		371613	407953	18500	6.0	0.0278	24.94	0.93	0.91	1.02	1.00	1.46
125		334591	352924	28900	5.0	0.0381	18.18		344739	363148	29400	5.5	0.0405	17.13	0.95	0.95	0.97	0.97	0.98
126		734010	790604	63000	4.5	0.0313	22.16		543428	568077	40100	6.0	0.0434	15.97	0.93	0.96	1.35	1.39	1.57
127		296992	317746	19900	5.0	0.0358	19.36		232298	270933	15400	6.0	0.0224	30.92	0.93	0.86	1.28	1.17	1.29
MEAN	527	437568	462609	37525	5.0	0.0358	20.35	534	433728	465788	36921	4.9	0.0343	22.62	0.94	0.927	1.02	1.00	1.05
SD	214	229910	233615	19057	1.1	0.0073	5.46	171	223456	225706	18216	1.1	0.0097	9.92	0.03	0.059	0.19	0.18	0.3
%CV	41	53	50	51	23	20	27	32	52	48	49	23	28	44	3	6	19	18	29
MIN																			
MAX																			

TABLE 3B: ESTRONE SULFATE parametric data based on plasma concentrations *corrected* for baseline values. ANDA #40-135, Fasting study

	TEST			REF			AUC/ AUCinf		TEST/ REF		
SUBJ	AUC	AUCinf	Cmax	AUC	AUCinf	Cmax	TEST	REF	AUC	AUCinf	Cmax
101	533973	547008	47687	429831	455603	30518	0.98	0.94	1.24	1.20	1.56
102	332899	336195	35434	319276	319381	36767	0.99	1.00	1.04	1.05	0.96
103	367920	381229	27151	300893	316716	24463	0.97	0.95	1.22	1.20	1.11
104	357343	382065	38894	690059	708785	66529	0.94	0.97	0.52	0.54	0.58
105	209591	212157	20767	208558	209562	33427	0.99	1.00	1.00	1.01	0.62
106	357303	361714	22225	374406	388979	26456	0.99	0.96	0.95	0.93	0.84
107	1291226	1295698	106021	1285315	1303202	101097	1.00	0.99	1.00	0.99	1.05
108	241358	249941	31970	378816	389069	38229	0.97	0.97	0.64	0.64	0.84
109	365140	370559	29620	365371	370728	31580	0.99	0.99	1.00	1.00	0.94
110	268803	270561	39329	276131	280309	51614	0.99	0.99	0.97	0.97	0.76
111	201156	205266	28727	214007	215467	32717	0.98	0.99	0.94	0.95	0.88
112	284406	288694	24558	246831	314602	29751	0.99	0.78	1.15	0.92	0.83
115	468089	474555	50384	323735	333655	29068	0.99	0.97	1.45	1.42	1.73
116	322267	324949	28961	313822	317707	30994	0.99	0.99	1.03	1.02	0.93
117	341764	352923	22648	312237	320288	21845	0.97	0.97	1.09	1.10	1.04
118	449644	458583	43166	420974	427259	29352	0.98	0.99	1.07	1.07	1.47
119	308303	320513	35592	371376	445930	32744	0.96	0.83	0.83	0.72	1.09
120	564660	572129	63462	537206	543943	60693	0.99	0.99	1.05	1.05	1.05
121	411787	436303	26654	424798	450639	27656	0.94	0.94	0.97	0.97	0.96
122	336232	352443	28024	372918	375631	36518	0.95	0.99	0.90	0.94	0.77
124	353877	371482	26742	331565	347864	17943	0.95	0.95	1.07	1.07	1.49
125	300462	306337	28425	309891	316340	28916	0.98	0.98	0.97	0.97	0.98
126	673458	703162	62159	499772	510453	39494	0.96	0.98	1.35	1.38	1.57
127	257067	262309	19345	197501	214559	14916	0.98	0.92	1.30	1.22	1.30
MEAN	399947	409866	36998	396054	411528	36387	0.97	0.96	1.03	1.01	1.06
SD	220441	221685	18965	219016	220480	18162	0.02	0.05	0.20	0.20	0.31
%CV	55	54	51	55	54	50	2	5	20	20	29
MIN											
MAX											

Table 4: Estrone plasma concentrations for the test and reference products (ANDA #40-135, Fasting Study)

Time	TEST		REF		TEST/REF
(hr)	CONC	CV(%)	CONC	CV(%)	
-48	39	33	40	36	0.96
-24	34	46	35	39	0.96
-0.25	35	35	38	24	0.94
1	190	57	163	66	1.16
2	425	53	402	48	1.06
3	603	48	574	47	1.05
3.5	700	46	667	45	1.05
4	770	48	712	41	1.08
4.5	808	37	779	40	1.04
5	820	36	827	37	0.99
5.5	929	39	896	41	1.04
6	901	40	856	36	1.05
7	811	38	786	41	1.03
8	792	35	696	39	1.14
10	593	36	572	41	1.04
12	476	31	474	39	1.00
16	349	34	336	41	1.04
24	218	38	224	45	0.97
30	176	41	174	46	1.01
36	151	44	145	42	1.04
48	98	41	100	37	0.97
60	70	41	74	40	0.95
72	56	41	67	39	0.84

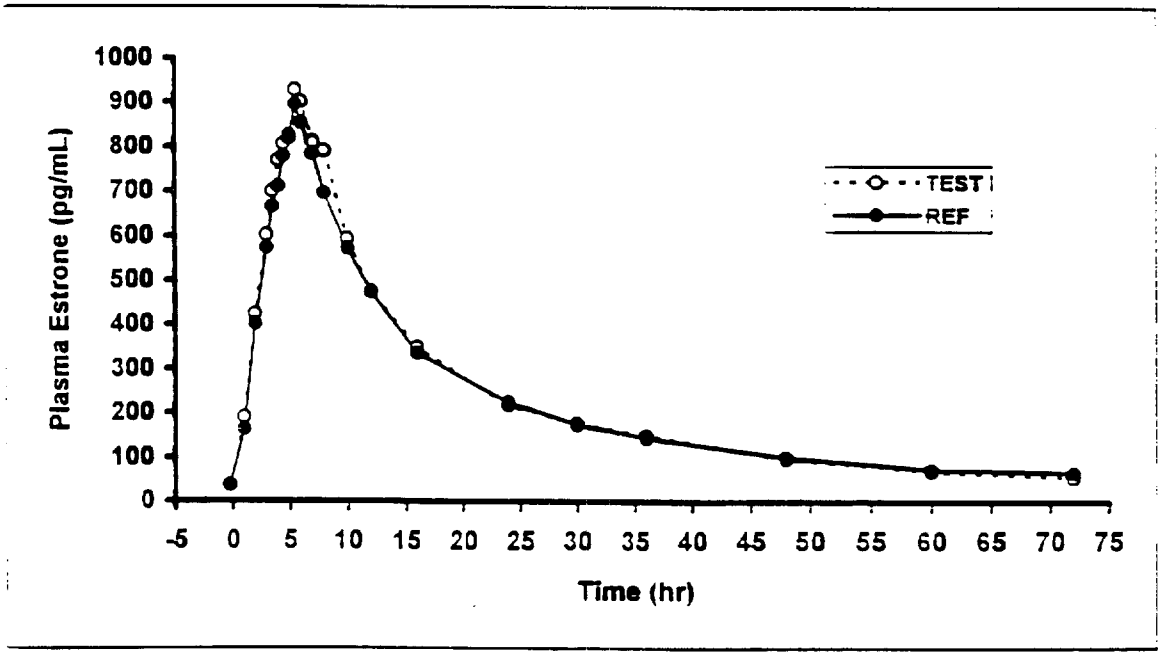

TABLE 5: Estrone Parametric data, ANDA #40-135, Fasting study

X: All subject's data analyzed as one

PARAMETER	TEST		REF		TEST/REF	90% CI*
	Mean	%CV	Mean	%CV		
	Based on uncorrected data					
AUC (pg/mL*hr)	16750	34	16416	34	1.02	94.68 - 108.09
AUCinf (pg/mL*hr)	18645	33	20043	35	0.93	83.05 - 102.52
Cmax (pg/mL)	987	37	987	37	1.00	93.11 - 106.68
Tmax (hr.)	5.9	19	5.5	18	1.07	
kel (1/hr)	0.032	20	0.029	32	1.10	
t1/2 (hr)	22.8	25	31.5	86	0.72	
	Based on data corrected for baseline values					
AUC (pg/mL*hr)	14148	37	13705	40	1.03	94.87 - 112.68
AUCinf (pg/mL*hr)	14890	37	15677	40	0.95	84.78 - 107.23
Cmax (pg/mL)	951	38	949	39	1.00	93.28 - 107.5
	Y: Data from Groups A (sub #101-107) and B (sub 108-127) analyzed separately					
	Group A: Based on uncorrected data					
AUC (pg/mL*hr)	18331	30	16356	45	1.12	98.33 - 137.09
AUCinf (pg/mL*hr)	19737	29	21447	48	0.92	73.23 - 121.52
Cmax (pg/mL)	1149	27	1053	38	1.09	94.56 - 126.63
	Group A: Based on data corrected for baseline values					
AUC (pg/mL*hr)	15984	33	14046	54	1.14	95.72 - 159.12
AUCinf (pg/mL*hr)	16564	32	17383	54	0.95	76.47 - 141.22
Cmax (pg/mL)	1116	28	1020	40	1.09	94.56 - 128.03
	Group B: Based on uncorrected data					
AUC (pg/mL*hr)	16099	35	16440	31	0.98	89.86 - 101.88
AUCinf (pg/mL*hr)	18196	35	19465	28	0.93	80.40 - 103.72
Cmax (pg/mL)	921	35	960	31	0.96	88.63 - 104.19
	Group B: Based on data corrected for baseline values					
AUC (pg/mL*hr)	13392	38	13565	34	0.99	89.81 - 103.12
AUCinf (pg/mL*hr)	14201	39	14974	21	0.95	80.62 - 105.16
Cmax (pg/mL)	883	41	920	39	0.96	88.71 - 104.75

** 90% CI are based on ANOVA performed by reviewer using the log transformed parametric data*

TABLE 6A: Estrone parametric data based on plasma concentration *not* corrected for baseline values. ANDA #40-135, Fasting study

	TEST							REF							AUC/ AUCInf		TEST/ REF		
SUBJ	BL	AUC	AUCINF	Cmax	Tmax	Kel	T1/2	BL	AUC	AUCINF	Cmax	Tmax	Kel	T1/2	TEST	REF	AUC	AUCinf	Cmax
101		15922	17418	802	5 5	0 034	20 2		12704	37644	781	7 0	0.006	124.4	0.91	0.34	1.25	0.46	1.03
102		19425	20860	1260	5.5	0.037	18 7		12714	14384	792	3.5	0.029	23.72	0.93	0.88	1.53	1.45	1.59
103		20703	21859	1370	5.5	0.039	18		15200	16107	923	4.5	0.035	19.59	0.95	0.94	1.36	1.36	1.48
104		16977	18481	1170	5.5	0.036	19.2		18931	21430	1230	4.5	0.033	21.15	0.92	0.88	0.90	0.86	0.95
105		8952	9499	724	5.0	0.031	22 7		6119	8161	583	4.0	0.018	38.36	0.94	0.75	1.46	1.16	1.24
106		19219	21318	1090	6.0	0.032	21.6		18964	20709	1310	7.0	0.035	19.96	0.90	0.92	1.01	1.03	0 83
107		27121	28722	1630	7.0	0 037	18.9		29861	31691	1750	4.0	0.036	19.31	0.94	0.94	0.91	0.91	0.93
108		10262	12491	719	7.0	0.018	39.1		11649	14231	836	7.0	0.017	39.77	0.82	0.82	0.88	0.88	0.86
109		12757	13891	570	6.0	0.036	19 3		13193	15313	512	5.5	0.032	21.93	0.92	0.86	0.97	0 91	1 11
110		13808	14726	993	4.0	0.041	17.1		17021	18149	996	5.5	0.041	16.85	0.94	0.94	0 81	0.81	1.00
111		14996	17208	1140	6.0	0.024	28.9		13329	14909	1330	5.5	0.03	23.39	0.87	0.89	1.13	1.15	0.86
112		7053	8623	460	5.5	0 027	25.3		10598	26405	687	5.5	0.006	109.8	0.82	0.40	0.67	0.33	0.67
115		17102	18330	1100	6.0	0.038	18.3		16984	19233	878	5.0	0.032	21.44	0.93	0.88	1.01	0.95	1.25
116		14759	16593	780	5.5	0.027	25.4		12802	14469	709	5.5	0.028	25.23	0.89	0.88	1.15	1.15	1.10
117		9045	9797	606	5.5	0 041	17.1		11530	12522	794	6.0	0.036	19.42	0.92	0.92	0.78	0.78	0.76
118		17675	22283	858	5 5	0.019	37 5		18008	21491	774	6.0	0.026	27.09	0.79	0.84	0.98	1.04	1.11
119		29306	32791	1980	6.0	0.028	24.9		30160	32853	1610	5.5	0.035	19.75	0.89	0.92	0.97	1.00	1.23
120		18814	20432	1120	3.5	0.035	20		16480	17831	1620	5.5	0.038	18.44	0.92	0.92	1.14	1.15	0.69
121		14415	15740	651	8.0	0.033	21		15345	17718	628	6.0	0.028	25.18	0.92	0.87	0.94	0.89	1.04
122		11729	13388	587	6.0	0 032	21.5		13408	15065	623	7.0	0.033	21.35	0.88	0.89	0.87	0.89	0.94
124		16285	17922	757	8.0	0.03	22.9		15521	18680	610	6.0	0.022	32.11	0.91	0.83	1.05	0.96	1.24
125		19696	21530	1200	6.0	0.035	20 1		17973	19977	1210	6.0	0.033	21.24	0.91	0.90	1.10	1.08	0 99
126		26092	28675	1260	4 5	0 034	20 5		24496	27906	1510	5 0	0.029	23.73	0.91	0.88	1.07	1 03	0 83
127		19886	24912	870	8.0	0 025	28 3		20987	24154	998	5.0	0.03	22.91	0.80	0.87	0.95	1.03	0 87
MEAN	36.1	16750	18645	987	5.9	0 032	22.8	37.8	16416	20043	987	5.5	0.029	31.5	0.90	0.84	1.04	0.97	1.03
SD	11.6	5613	6155	362	1.1	0.006	5.8	11.2	5648	7019	369	1.0	0.009	27.0	0.05	0.15	0.21	0.24	0.23
%CV	32	34	33	37	19	20	25	30	34	35	37	18	32	86	5	18	20	25	22
MIN																			
MAX																			

TABLE 6B: Estrone parametric data based on plasma concentration *corrected* for baseline values. ANDA #40-135, Fasting study

	TEST (BC)			REF (BC)			AUC/ AUCinf		TEST/ REF		
SUBJ	AUC	AUCinf	Cmax	AUC	AUCinf	Cmax	TEST	REF	AUC	AUCinf	Cmax
101	13843	14499	773	10384	29540	749	0.95	0.35	1.33	0.49	1.03
102	16788	17231	1223	9954	10311	754	0.97	0.97	1.69	1.67	1.62
103	18491	18848	1339	13431	13644	898	0.98	0.98	1.38	1.38	1.49
104	15036	15791	1143	17157	18905	1205	0.95	0.91	0.88	0.84	0.95
105	7049	7509	697	3177	3302	538	0.94	0.96	2.22	2.27	1.30
106	15953	16641	1045	16744	17600	1279	0.96	0.95	0.95	0.95	0.82
107	24731	25429	1597	27472	28376	1717	0.97	0.97	0.90	0.90	0.93
108	7884	8249	686	9566	10487	807	0.96	0.91	0.82	0.79	0.85
109	9691	10213	529	8938	9186	453	0.95	0.97	1.08	1.11	1.17
110	12048	12365	969	15176	15681	970	0.97	0.97	0.79	0.79	1.00
111	12951	13978	1112	10874	11303	1296	0.93	0.96	1.19	1.24	0.86
112	5301	5983	436	8078	18342	652	0.89	0.44	0.66	0.33	0.67
115	15007	15466	1071	14505	15689	844	0.97	0.92	1.03	0.99	1.27
116	11515	11695	735	10539	11062	678	0.98	0.95	1.09	1.06	1.08
117	8363	8881	596	9891	10245	771	0.94	0.97	0.85	0.87	0.77
118	14164	16128	809	14885	16670	731	0.88	0.89	0.95	0.97	1.11
119	25506	27091	1927	26349	27533	1557	0.94	0.96	0.97	0.98	1.24
120	16422	17082	1087	14027	14472	1586	0.96	0.97	1.17	1.18	0.69
121	12101	12454	619	13053	14269	596	0.97	0.91	0.93	0.87	1.04
122	8061	8144	536	10094	10333	577	0.99	0.98	0.80	0.79	0.93
124	13813	14317	723	12699	14043	571	0.96	0.90	1.09	1.02	1.27
125	16411	16925	1154	15121	15912	1170	0.97	0.95	1.09	1.06	0.99
126	21559	22277	1197	20376	21823	1453	0.97	0.93	1.06	1.02	0.82
127	16859	20165	828	16436	17511	933	0.84	0.94	1.03	1.15	0.89
MEAN	14148	14890	951	13705	15677	949	0.95	0.90	1.08	1.03	1.03
SD	5190	5451	358	5451	6315	369	0.04	0.16	0.33	0.38	0.24
%CV	37	37	38	40	40	39	4	18	30	37	23
MIN											
MAX											

BC = Baseline corrected.

Table 7: *In vitro* Dissolution Testing

)rug (Generic Name): **Estropipate Tablet**
)ose Strength: 3 mg, 1.5 mg and 0.75 mg
NDA # 40-135
'irm. Barr Laboratories
ubmission Date: February 9, 1995
'ile Name: **40135SD.O96**

Conditions of in vitro dissolution testing:

USP XXII Paddle. RPM: 75
No. Units tested: 12
Medium: 900 mL Water
Specification: NLT Q) in 60 minutes
Reference Drug : Ogen Tablet , 3 mg, manufactured by Abbot Laboratories.

. **Results of *In vitro* dissolution testing:**

Sampling Time (min)	Test Product Lot # 4R72903 Strength: 3 mg			Reference Product Lot # 73-820-AA-21 Strength: 3 mg		
	Mean (%)	Range (%)	CV (%)	Mean (%)	Range (%)	CV (%)
5	98		5.4	103		1.5
10	104		2.5	103		1.1
20	104		2.7	103		1.5
30	104		3.0	102		1.4
45	104		2.3	103		1.6
60	104		2.4	103		1.1

Sampling Time (min)	Test Product Lot # 4R72732 Strength: 0.75 mg			Reference Product Lot # 394MJ Strength: 0.75 mg		
	Mean (%)	Range (%)	CV (%)	Mean (%)	Range (%)	CV (%)
5	101		2.9	99		1.0
10	102		2.4	99		1.0
20	102		2.4	99		1.2
30	102		2.5	99		1.3
45	102		2.4	99		1.1
60	102		2.6	99		1.1

Sampling Time (min)	Test Product Lot # 4R72833 Strength: 1.5 mg			Reference Product Lot # 84-661-AA-21 Strength: 1.5 mg		
	Mean (%)	Range (%)	CV (%)	Mean (%)	Range (%)	CV (%)
5	102		3.5	101		2.6
10	102		1.2	101		2.1
20	102		1.9	101		2.0
30	101		2.3	101		1.7
45	100		2.9	101		1.4
60	101		2	102		2.0